Synthesis of quercitols and inosamines(Dissertation_全文)

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SYNTHESIS OF QUERCITOLS AND INOSAMINES

京都大学審査博士学位論文

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1961

ACKNOWLEDGMENT

This study was carried out from April 1956 to March 1961 in the laboratory of Agricultural Chemicals under the guidance of Former Professor S.Takei and Professor M.Nakajima, to whom the author wishes to express his sincere appreciation.

He is also thankful to Mr. I.Tomida for his guidance throughout the course of this work and to Mr. A.Hasegawa for his skilful and energetic experimental work in the synthetic study of inosamines.

The author is indebted to Assistant Professor Z.Kumazawa and to Mr. H.Fukami for their helpful discussions and suggestions; and to all other members in the laboratory of Agricultural Chemicals, in the laboratory of Technology of Agricultural Products and in the laboratory of Insect Control in the Institute for Chemical Research for their infrared analyses, elemental analyses and many helps during the work. To all these people above, the author expresses his deep gratitude.

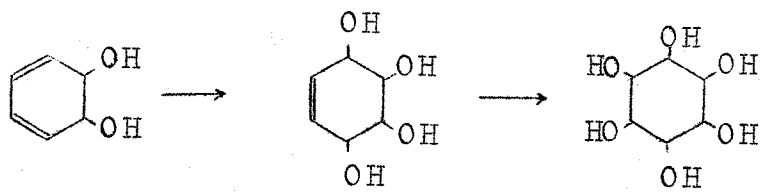
I. Introduction

Polyhydroxycyclohexanes are generally called cyclitols including inositol (1,2,3,4,5,6-hexahydroxycyclohexane), quercitol (1,2,3,4,5-pentahydroxycyclohexane) etc. They have been attracting many chemists' attention, since those compounds have wide distributions in nature and some of them are believed to play an important role in the physiological action of animals, plants and microörganisms. For example, myo-inositol, one of the inositol stereoisomers, exists in animals and plants, e.g. in the forms of polyphosphate ester, methyl ether and so on[1]. It has some nutritional action on animals and yeasts, and its metabolic studies are now going on in several laboratories. Cyclitol derivatives such as inosamine (aminodeoxyinositol) are also interesting substances, as some of them are found to be components of such important antibiotics as streptomycins[2], neomycin[3], kanamycins[4], hygromycins[5] and paromomycin.[6]

Not only biochemists but organic chemists

have been also interested in such biochemically significant compounds, and still now those people are active on the synthetic problem of these compounds, which also offer many stereochemically important facts.

Benzeneglycols———cis- and trans-5,6-dihydroxycyclohexadiene-1,3———synthesized by M. Nakajima et al.[7)8)] several years ago proved themselves excellent starting materials to prepare various cyclitols. For example, on stepwise hydroxylation, they gave conduritols (3,4,5,6-tetrahydroxycyclohexene-1) and inositols.



BENZENEGLYCOL CONDURITOL INOSITOL

In participating this work, the author synthesized also several stereoisomers of quercitol (deoxyinositol) and inosamine through novel routes, which will be described precisely in the following chapters.

II. Benzeneglycols, Conduritols and Inositols.

1. Benzeneglycols

Benzeneglycols are synthesized from BTC (benzene tetrachloride)(3,4,5,6-tetrachlorocyclohexene-1)(I).

BTC was prepared by Calingaert et al[9], which had been assumed to be an intermediate in the production of BHC from benzene but could not be isolated by normal technics. Using iodine as negative catalyst of the additive chlorination, they carried out the photochlorination of benzene to obtain the mixture of polychlorinated cyclohexenes from which the substance of m.p.33.5° was isolated after rectifications and recrystallizations. This is an isomer of BTC and is named α-BTC, the conformation of which was determined as $\overline{\text{H}}$Heeaa.

M.Nakajima and co-workers including the author oxidized this substance with CrO_3 to epoxide (II)[10] and with $KMnO_4$ to cis-dihydroxy-compound (III)[8].

When BTC was heated vigorously with CrO_3 in acetic acid for a few minutes, it gave a product

of m.p.90° which was proved to be α-1,2-epoxy-3,4,5,6-tetrachlorocyclohexane (α-BTC epoxide)(II). For this compound, two diastereomers epimeric at C-1 and C-2 are possible but it has not been determined yet which isomer corresponds to the epoxide obtained. This epoxide is so stable against the hydrolytic action that it must be heated with 50% H_2SO_4 for preparing 3,4,5,6-tetrachlorocyclohexanediol-1,2 (trans-BTC diol), m.p. 138° (IV), and in this case, Walden inversion occurred at C-1 or C-2.

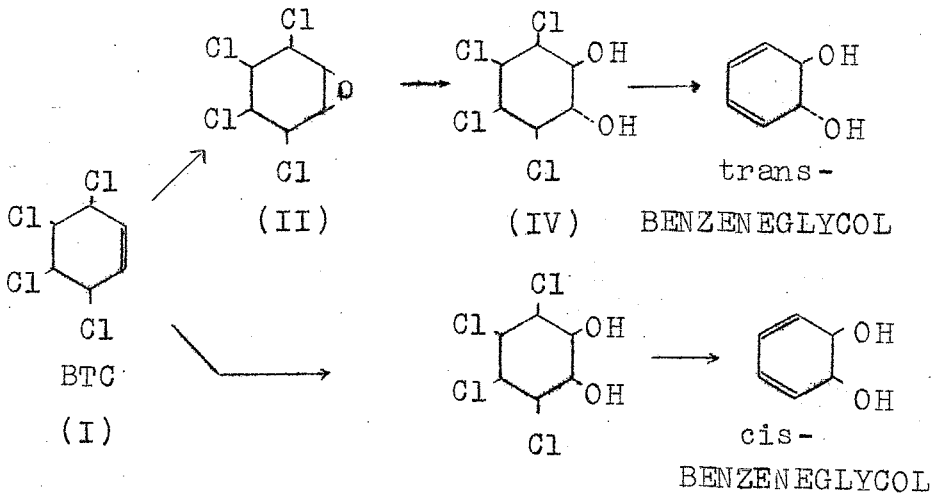
trans-BTC diol was converted to the chlorine free substance by vigorous stirring with zinc power in hot water. trans-Benzeneglycol(V) was thus obtained as leaflets melting at 74°.

On permanganate oxidation, BTC gave tetrachloroadipic acid at higher temperature[10], but with cooling and in the neutral medium a neutral substance of m.p.140°———3,4,5,6-tetrachlorocyclohexanediol-1,2 (cis-BTC diol)[8](III). (The cis-glycol group is probably situated trans to the neighboring chlorine atoms, as one molar dehydrochlorination———trans-elimination———yields

1,2-epoxy-3-hydroxy-4,5,6-trichlorocyclohexane; m.p.116°, m.p. of monoacetate 143°). The diol melted about at the same point with trans isomer but the mixed m.p. showed clear depression. The diol gave cis-benzeneglycol(VI) of m.p.60° on dechlorination with zinc under similar condition as trans isomer.

Fig. 1.

Synthesis of Benzeneglycols



Some physical properties of benzeneglycols are listed in the following table.

Table 1. Benzeneglycols

Benzeneglycol	M.p.	λ max	log ε	B.p. of Ac_2
trans	74°	262mμ	3.49	89° /1mmHg
cis	60°	262mμ	3.57	98° /2mmHg

Both isomers of benzeneglycol are easily soluble in water and in alcohol, and on hydrogenation each isomer gave the corresponding stereoisomer of cyclohexane-diol. Benzeneglycol suffered dehydration to phenol easily; especially, cis-isomer is so unstable that, on standing in weakly acidic medium, it changes rapidly and quantitatively to phenol, though it is rather stable in alkaline solution.

2. Conduritols.

In 1908, Kubler[11] isolated an isomer of 3,4,5,6-tetrahydroxycyclohexene-1(m.p.143°) from the bark of the vine Marsdenia condurango and named "conduritol". Later, Dangschat and Fischer[12] induced its conformation as $\overline{\text{HH}}$eeaa from the oxida-

tion products such as muco-inositol, allo-inositol and allo-mucic acid.

There are six separable forms in 3,4,5,6-tetrahydroxycyclohexene-1, its ten theoretically possible isomers being reduced on the basis of ring conversion. (Table 2 and Fig. 2)

Table 2.

3,4,5,6-Tetrahydroxycyclohexenes-1(Conduritols)

Conduritol	M.p.	M.p. of Ac_4	Conformation
A	142-143°	(163°/0.5mmHg)	$\overline{\overline{HH}}$aaee(⇌$\overline{\overline{HH}}$eeaa, i. identity)
B	204.5-205°	92-93°	$\overline{\overline{HH}}$eeee⇌$\overline{\overline{HH}}$aaaa
C	151.5-152.2°	90-92°	$\overline{\overline{HH}}$eaee⇌$\overline{\overline{HH}}$aeaa
D	ca. 62°	103-103.5°	$\overline{\overline{HH}}$eaea(⇌$\overline{\overline{HH}}$aeae, i. identity)
E	179-180°	152.5-153°	$\overline{\overline{HH}}$aeea⇌$\overline{\overline{HH}}$eaae
F	103-104°	92°	$\overline{\overline{HH}}$aeee⇌$\overline{\overline{HH}}$eaaa

Fig. 2 Conduritols

(See the next page.)

(Only the bond to which a hydroxyl group is attaching is shown in this figure and also in the other formulae appearing in this paper.)

A B C D E F

Thanks to works of McCasland, Angyal and Criegee, and also to the recent researches in Kyoto, all those isomers are now synthetically known and called "conduritols" as the generic name. Each isomer is distinguished from others by adding alphabetical suffix; for example the natural conduritol isolated by Kubler is named conduritol-A and the newest one synthesized from cis-benzeneglycol conduritol-F.

By now, the following synthetic methods of conduritols are known.

(1) From bromodeoxyinositols. McCasland and Horswill[13] obtained two bromodeoxyinositols by heating myo-inositol with acetyl bromide in a sealed tube and, by debromination of their pentaacetate

with zinc, prepared an acetylated tetrol of m.p.93° which was ammonolyzed to a new unsaturated tetrol (m.p.205°) named conduritol-B. Its configuration was established by hydrogenation to a known cyclohexanetetrol(all trans).

In a similar way, McCasland and Reeves[14] prepared conduritol-C from epi-inositol.

(2) From di-O-arenesulfonyl derivatives of inositols. Angyal and Gilham[15] prepared the di-O-arenesulfonyl derivatives of two inositols, l- and epi-, and heated their di-O-isopropylidene derivatives with sodium iodide in acetone in sealed tubes, obtaining an optically active conduritol (an optical isomer of conduritol-E) and all-cis isomer (conduritol-D).

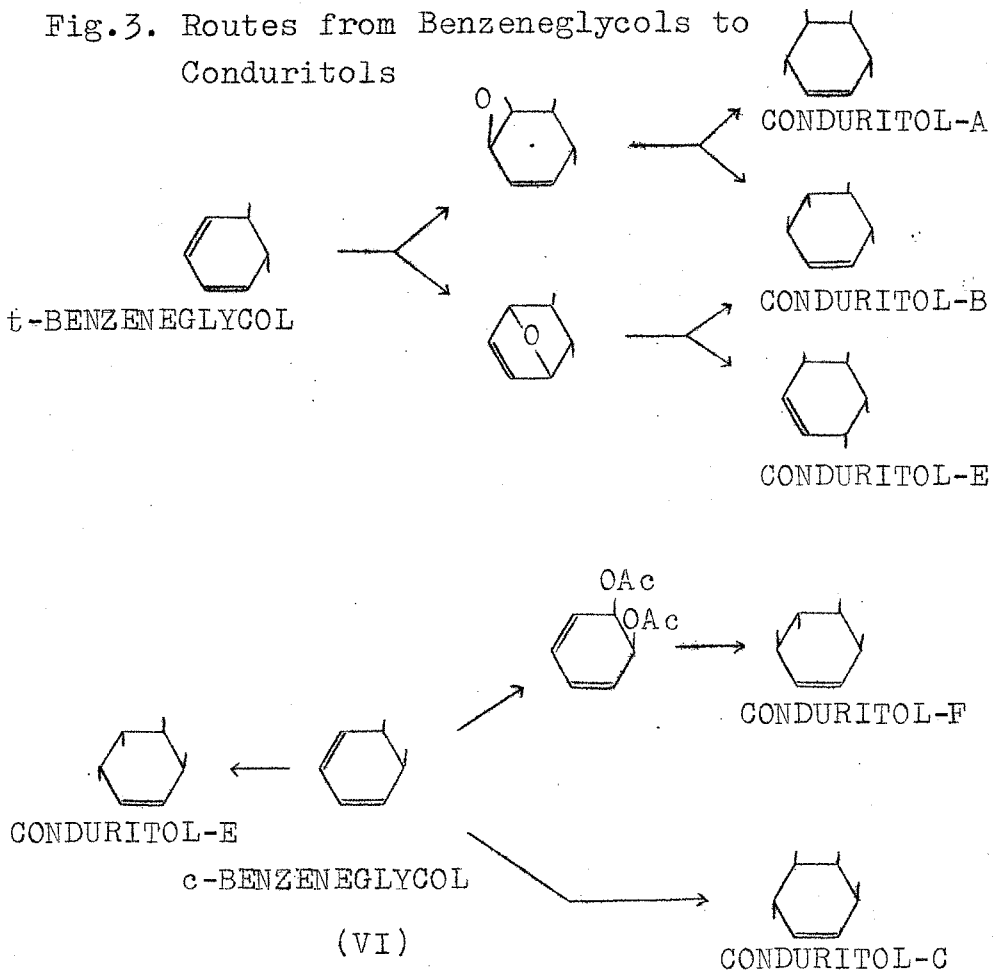
(3) By a diene synthesis. Recently, Criegee and Becher[16] synthesized conduritol-D using trans, trans-diacetoxybutadiene as a diene compound, and vinylenecarbonate as a dienophile. The addition proceeded at 205-210° in an autoclave. The adduct thus obtained on hydrolysis with $Ba(OH)_2$ gave conduritol-D as a syrup which crystallized after standing for several months on P_2O_5, but did not show a sharp melting point (about 62°).

(4) From benzeneglycols.[8)17)] trans-Hydroxylation of diacetate of trans-benzeneglycol gave conduritol-E in 16.5%, and -B in 3.5% yield. Conduritol-A was also obtained. It is the first synthesis of natural conduritol since its discovery in the beginning of this century. The yield, however, is very low, and an improved method was developed. When trans-benzeneglycol was allowed to react with perbenzoic acid in water, conduritol-A formed in much higher yield——40%. In spite of certain improvements, yields of other conduritols were lower; conduritol-E, 5%; conduritol-B, trace.

Conduritol-E has the conformation of $\overline{\overline{\text{HH}}}$aeea $\rightleftharpoons$ $\overline{\overline{\text{HH}}}$eaae which is the racemic compound of the active conduritol prepared by Angyal and Gilham. The formation of this isomer from trans-benzeneglycol confirms the existence of 1,4-epoxide as an intermediate.

cis-Benzeneglycol diacetate, on permanganate oxidation (cis-hydroxylation), gave conduritol-E in a fairly high yield. The all-cis conduritol has not been isolated from the resulted syrup although the formation of this isomer is theoretically possible.

Fig.3. Routes from Benzeneglycols to Conduritols



On the other hand, trans-hydroxylation of cis-benzeneglycol gave conduritol-C accompanied by very small amount of conduritol-F. When it was allowed to react as diacetate, conduritol-F tetraacetate was obtained in rather high yield, which

was deacetylated to conduritol-F.

Silver chlorate and osmium tetroxide were used for the cis-hydroxylation of trans-benzeneglycol. From the resulted material, conduritol-C was isolated as its tetraacetate.

The structures of conduritol-E and -F were determined by hydrogenation to the known saturated tetrols which had been prepared from 3,4-dihydroxycyclohexene-1 by Posternak and Friedli[18].

The highest yields of conduritol isomers from benzeneglycols are listed below.

Table 3. Yields of Conduritols

Benzeneglycol	Conduritol (%)					
	A	B	C	D	E	F
cis-	0(c)	-	34(t)	0(c)	51(c)	22(t)
trans-	40(t)	6(t)	24(c)	-	25(t)	0(c)

(c) cis-, (t) trans-hydroxylation

3. Inositols and Conduritol Epoxides.

One of the inositol isomers, myo-inositol, was isolated from the muscle of oxes at first.

Later, this isomer was found in many kinds of plants and animals, and various kinds of investigation on it have been continuing since then[1]. In 1942, its configuration was established by Posternak[19] and Dangschat[20], who oxidized it to obtain some derivatives.

scyllo-Inositol and methyl ethers of (+)- and (-)- inositol are also naturally occurring isomers[1], but the other inositols are only synthetically known. They were synthesized from aromatic compounds[21)-24], from nitrodeoxyaldoses[25)26], from inososes[27)-30], and also from the natural conduritol[12].

The following table shows the melting points and conformations of inositols and their hexaacetates.

Recently, stereospecific preparation from conduritols of all the inositol isomers except cis-inositol was attained in our laboratory. Cis- and trans-hydroxylation were carried out according to the methods of Dangschat and Fischer[12] who obtained muco- and allo-inositol from natural conduritol, and of Schöpf[31] who prepared the epoxide

Table 4. Inositols.

Inositol	M.p.	M.p. of Ac_6	Conformation
allo-	ca.320°dec.	144°	aaeaee(⇌eeaeaa, i.e.,d⇌l)
cis-	377°dec.	208°	aeaeae(⇌eaeaea, i.e.,identity)
epi-	304°dec.	188°	aeaeee ⇌ eaeaaa
muco-	ca.300°dec.	178°	aaaeee(⇌eeeaaa, i.e.,identity)
myo-	225°	217°	aeeeee ⇌ eaaaaa
neo-	315° dec.	253°	aeeaee ⇌ eaaeaa
rac-	253°	112°	aaeeee ⇌ eeaaaa
scyllo-	355°	301°	eeeeee ⇌ aaaaaa

of conduritol-A.

The yields of the inositols obtained from conduritols by this method are listed in the next page.

Table 5. Yields of Inositol Hexaacetates

Conduritol	Inositol Hexaacetate						
	allo- XIII	epi- XIV	muco- XV	myo- XVI	neo- XVII	rac- XVIII	scyllo- XIX
A	0(c)		60(c)			59(t)	
B				65(c)		44(t)	3(t)
C	54(t)	24(c)*		3(t)	20(c)**		
E	45(c)				44(t)	27(t)	
F		0(c)	15(t)	0(t)		69(c)	

* In aq. acetone. ** In aq. dioxane.

In the course of this work, the following conduritol epoxides were prepared. (see Table 6.) Five of them were unknown isomers and their configurations are discussed in the following chapter.

Table 6. Conduritol Epoxides (Anhydroinositols)

Cond. Epox.(Anhydroinositol)	M.p.	M.p. of Ac_4
A(2,3-anhydro-allo-)(VII)	112°	118.5°
B(1,2-anhydro-myo-)(VIII)	155°	126°
C(1,2-anhydro-neo-)(IX)	146°	115°
C(1,2-anhydro-epi-)(X)	(syrup)	116.5°
E(1,2-anhydro-allo-)(XI)	176°, 189°	117°
F(2,3-anhydro-epi-)(XII)	157.5°	130°

Experimental

(i) Benzeneglycols

Chromic acid oxidation of BTC(I).——To 120 ml of glacial acetic acid solution containing 15 g of BTC, 12 g of chromic anhydride were added, and the solution was heated at 100° with occasional shaking. When small bubbles appeared, the shaking became unnecessary, as the reaction followed smoothly. Constant and violent boiling continued for about 5 minutes and heating was stopped, $NaHSO_3$ was added

to consume excess chromate ion. Green colored solution thus obtained, on steam distillation, gave 1.4 g of BTC epoxide, m.p.90°(prisms)(II), and ca,8g of recovered material.
Anal. Calcd. for $C_6H_6Cl_4O$(235.9): C,30.54;H, 2.56;Cl,60.11.Found: C,30.61;H,2.77;Cl,59.96.

Hydrolysis of BTC epoxide (II).——Ten grams of BTC epoxide were heated at 100° in 300 ml of 50% H_2SO_4 with continuous stirring for 7 hours. After dilution with water, the slightly turbid solution was extracted continuously with ether. On evaporation of ether, 10 g of crude cyystals were obtained (93%). It melted at 133-137°. On recrystallization from chloroform, there were obtained analytically pure substance, m.p.137.5°-138°(plated)(IV). Anal. Calcd. for $C_6H_6Cl_4O_2$ (254.0): C,28.38;H,3.18;Cl,55.85. Found: C,28.66; H,3.16;Cl,55.80.

Dechlorination of trans-BTC diol(IV)(Preparation of trans-benzeneglycol(V).——In a mortar,

5 g of trans-BTC diol were mixed thoroughly with 10 g of zinc powder. The mixture in 40 ml of water was vigorously stirred for 30 minutes at 60°. Undissolved materials including zinc powder were filtered off from the hot reaction mixture, and the filtrate extracted continuously with ether. After about 10 hours, 2.0 g (quantitative) of crude trans-benzeneglycol (V) were obtained, m.p.71-73°. Recrystallization from benzene raised the melting point to 73-74° (leaflets). Anal. Calcd. for $C_6H_8O_2$(112.1):C,64.27;H,7.19. Found: C,64.19; H,7.09.

trans-Benzeneglycol diacetate.——One gram of trans-benzeneglycol (V) was dissolved in 3 g of pyridine, and to the solution 5 g of acetic anhydride were added with cooling with ice-water. After 24 hours, the solution was poured onto crushed ice and extracted with ether. The ethereal solution was washed with 2N-H_2SO_4 and then sat-$NaHCO_3$ solution, dried and evaporated to give 1.42 g of diacetate as a colorless oil (81%), b.p. 112°/5mmHg.

Permanganate oxidation of BTC(I).——One hundred and twenty ml of ethanol solution of 2.20 g of BTC were mixed with 20 ml of aqueous solution of 3.0 g of $MgSO_4$, and there were added 3.20 g of $KMnO_4$ in 200 ml of water drop by drop at 1.5-4.0° with continuous stirring. Agter about a half volume of the permanganate solution was added, the mixture of 20 ml of aqueous solution of 3.0 g of $MgSO_4$ and 120 ml of ethanol were added. After standing overnight, MnO_2 was filtered off, washed with ethanol and the filtrate concentrated and extracted with ether. The ethereal layer on evaporation gave crude crystals which were recrystallized from chloroform giving 1.31 g(62%) of cis-BTC diol, m.p.140°(prosms)(III). Anal. Calcd. for $C_6H_8Cl_4O_2$(254.0): C,28.38;H,3.18;Cl,55.85. Found: C,28.48;H,3.45;Cl,56.11.

Dechlorination of cis-BTC diol(III)(Preparation of cis-benzeneglycol(VI)).——cis-BTC diol (2.89 g) was mixed with 6 g of zinc powder and 60 ml of water. The mixture was vigorously stirred at 55°. Then the exothermic reaction occurred

and the temperature began to rise very quickly. At that time it was necessary to maintain the temperature below 65°, as otherwise the formation of phenol was remarkable. After 10 minutes more heating, undissoved materials were filtered off and 4N-NaOH was added to alkalize the filtrate. Ethereal extract of the filtrate was dried and evaporated giving 1.16 g(90%) of crude cis-benzeneglycol, m.p.49°(VI). Recrystallization from n-hexane raised the m.p. to 60° (leaflets). Anal. Calcd. for $C_6H_8O_2$(112.1): C,64.27;H,7.10. Found: C,64.19;H,7.44.

cis-Benzeneglycol diacetate.——To the solution of 1.23 g of cis-benzeneglycol(VI) in 5 g of pyridine, 6 g of acetic anhydride were added in portion with cooling. After standing overnight, the mixture was poured onto crushed ice. The whole solution was extracted with ether, and washed with dilute H_2SO_4, water, sat-$NaHCO_3$ and then water. The ethereal layer was dried over Na_2SO_4 and evaporated to give an oily residue.

It boiled at 97-98°/2mmHg, and weighed 1.78 g(83%).

(ii) Conduritols

Perbenzoic acid oxidation of trans-benzeneglycol(V)(Preparation of conduritol-A, -B and -E).

(i) In aqueous solution.——Five hundred milligrams of trans-benzeneglycol dissolved in 50 ml of water were added with cooling to 100 ml of aqueous perbenzoic acid solution (containing 720 mg, 1.25 moles equiv.). After three days standing at room temperature the precipitated benzoic acid was filtered off and the filtrate washed with ether. The aqueous layer was dried up in vacuo to give 740 mg of a syrup which was chromatographed on an alumina column (activity:1, 1.5cm x 21cm) in absolute methanolic solution or on a cellulose powder column (4.5cm x 40cm) in aceton/water(4:1) solution. Conduritol-A was the first component to come off the column and conduritol-E and -B followed. The fractions containing conduritol-A (detected by paper chromatography) were collected and dried up to give a colorless syrupy residue. Extracted with boiling

dry acetone (or ethanol), and cooled in the refrigerator, it crystallized and weighed 265 mg (m.p.120-130°). Recrystallized from ethanol, conduritol-A melted at 135°.

In a similar way, slower moving fractions gave 10 mg of conduritol-E (m.p.174-176°).

(ii) In chloroform solution.——One gram of trans-benzeneglycol diacetate in 5 ml of chloroform was added to 15 ml of chloroform solution of perbenzoic acid (containing 890 mg; 1.25 moles equiv.). After three days standing in the refrigerator, the solution washed with 2N-Na_2CO_3 and water and dried over Na_2SO_4. On distillation the solution gave 1.03 g of an oil, b.p.122-127°/1mmHg. When 1.54 g of the oil were warmed in 10 ml of water with 1 drop of 2N-H_2SO_4 on the steam bath, the oil was soon dissolved, and after cooled, the solution neutralized with 1 drop of 2N-Na_2CO_3 and evaporated to dryness. To the syrupy residue, 5 g of pyridine and 7.5 g of acetic anhydride were added. After standing overnight at room temperature, the mixture was poured onto

crushed ice. After extraction with ether and washing with 2N-H_2SO_4, water, sat-$NaHCO_3$ and water in turn, the ethereal layer was dried and the solvent evaporated. Four hundred and ninety milligrams of conduritol-E tetraacetate (m.p.152.5-153°) separated as plates. Anal. Calcd. for $C_{14}H_{18}O_8$(314.3): C,53.50;H,5.77. Found: C,53.60;H,5.93.

From the filtrate, 1.4 g of an oil(a)(b.p. 157-158°/1mmHg) were obtained.

Three hundred and twenty milligrams of conduritol-E tetraacetate were dissolved in 22 ml of a saturated solution of dry ammonia in absol. methanol. After standing overnight at room temperature and evaporating the solvent, acetamide was sublimed off from the residue at 70°/8mmHg. The residue, on recrystallization from absol. ethanol gave 0.10 g(67.5%) of conduritol-E, m.p. 179-180°(colorless plates).

A part (1.19g) of the oily mixture described above(a), after redistillation, was ammonolyzed with 40 ml of a saturated solution of dry ammonia in absol. methanol. After removal of the solvent and acetamide, the syrupy redidue was chromato-

graphed on an alumina column (1.5cm x 15cm) in abs. methanolic solution and washed with 90% aq. methanol. From the faster moving fractions, 0.11 g of a syrup, and from the slower moving fractions, 0.09 g of a syrup were obtained respectively. On extraction with hot acetone and recrystallization from absol. ethanol, the former syrup gave 60 mg of conduritol-A (m.p.140-141°) which did not show any depression when mixed with the natural conduritol. Anal. Calcd. for $C_6H_{10}O_4$(146.1): C,49.31;H,6.90. Found: C,49.51; H,7.29.

When the slower moving material was treated with absol. acetone, it gave 40 mg of conduritol-B(m.p.199-200°). Anal. Calcd. for $C_6H_{10}O_4$(146.1): C,49.31;H,6.90. Found: C,49.58;H,7.03.

Silver chlorate oxidation of trans-benzeneglycol (V)(Preparation of conduritol-C).——To 0.43 g of trans-benzeneglycol in 5 ml of water were added 5 ml of aqueous solution containing 0.21 g of silver chlorate and a few milligrams of

osmium tetroxide. The dark brown or black colored solution thus obtained was allowed to stand for 4 days in a dark place at room temperature. Then the precipitated silver chloride was filtered off and the filtrate, after washed with ether, evaporated to dryness in vacuo. A syrupy redidue (0.56 g) resulted to which 1.5 g of pyridine and 3 g of acetic anhydride were added. After standing overnight, the reaction mixture was poured into ice-water, extracted with ether and washed with 2N-H_2SO_4, water, sat-$NaHCO_3$ and again with water. On evaporation of ether after drying over Na_2SO_4, the extract gave 0.65 g of residue which was recrystallized from methanol to give 0.4 g (34.5%) of conduritol-C tetraacetate, m.p.92°. Anal. Calcd. for $C_{14}H_{18}O_8$(314.3): C,53.50;H,5.77. Found: C,53.58; H,5.92.

From 0.31 g of the tetraacetate, 0.1 g (70%) of crystalline conduritol-C were obtained by ammonolysis with 22 ml of a saturated solution of dry ammonia in absol. metahnol. A mixed m.p. of the crystals (m.p.146-149°) with ones synthesized by McCasland[13] was not depressed. Anal. Calcd.

for $C_6H_{10}O_4$(146.1): C,49.31;H,6.90. Found: C, 49.30;H,7.11.

Permanganate oxidation of cis-benzeneglycol diacetate (Preparation of conduritol-E).——To 65 ml of ethanolic solution of 1.38 g of the diacetate, 1.1 g of $MgSO_4$ in 10 ml of water were added. There were dropped in portion 110 ml of 1% $KMnO_4$ solution with vigorous stirring at -4 to -5°. When about a half volume of the permanganate solution was added, there was poured a cooled mixture of 65 ml of ethanol with 1.1 g of $MgSO_4$ in 10 ml of water. After standing overnight, MnO_2 was filtered off and the filtrate evaporated to dryness in vacuo. The residue was treated with 7 g of pyridine and 7 g of acetic anhydride. Recrystallization of the resulted material from ethanol gave 1.36 g (61%) of conduritol-E tetraacetate, m.p.149-150°. Anal. Calcd. for $C_{14}H_{18}O_8$(314.3): C,53.50;H,5.77. Found: C,53.79;H,6.07.

Perbenzoic acid oxidation of cis-benzeneglycol(VI)(Preparation of conduritol-C and -F). ——Oxidation was carried out in a similar way as described above.

(i) In aqueous solution: From 3.96 g of cis-benzeneglycol (divided in two portions) and total 5.86 g of perbenzoic acid in total 500 ml of water, 4.43 g of syrup were obtained. Dissolved in boiling ethanol and set aside at 10° to give 2.01 g of conduritol-C (m.p.137-144°). Recrystallized from ethanol to give 1.77 g of the pure substance (34.1%). A viscous syrup obtained from mother liquor of crude crystals gave, after acetylation, 0.622 g of conduritol-F tetraacetate (m.p.86.5°) (5.6%).

(ii) In chloroform solution: From 2.63 g of cis-beneneglycol diacetate and 2.20 g of perbenzoic acid in 57 ml of chloroform, an oily residue was obtained and hydrolyzed with 2N-H_2SO_4 to give 3 g of an oil. From the oil, 15 g of pyridine and 15 g of acetic anhydride, 2.84 g of a viscous oil were gained. Recrystallized from methanol. Giving 1.27 g of conduritol-F tetraacetate melting at 92°(colorless plates). Anal. Calcd. for $C_{14}H_{18}O_8$

(314.3): C,53.50;H,5.77. Found: C,53.35;H,5.74.

From the filtrate, 1.38 g of an oily substance were obtained.

From 0.32 g of the tetraacetate and 25 ml of ammonia saturated absol. methanol, 0.11 g of conduritol-F, m.p. 103-104°(plates) were obtained. Anal. Calcd. for $C_6H_{10}O_4$(146.1): C,49.31;H,6.90. Found: C,49.17;H,7.06.

(iii) Conduritol epoxides

Perbenzoic acid oxidation of conduritol-A: Eighty milligrams of conduritol-A(m.p.139-140°) in 6 ml of glacial acetic acid were mixed with 2.3 ml of chloroform solution of 128 mg of perbenzoic acid. After three days standing at room temperature, the solvent was evaporated in vacuo, and the residue washed with absol. ether several times. Then it was dissolved in a few milliliters of absol. ethanol and rubbed with cooling. Conduritol-A epoxide (m.p.111-112°)(VII) separated as colorless crystals.

Conduritol-B epoxide: Conduritol-B(0.1g), acetic acid (7 ml) and perbenzoic acid (0.16 g) in

chloroform (3 ml) gave conduritol-B epoxide, m.p. 154-155°.

Conduritol-C epoxide: Conduritol-C(0.1 g), acetic acid (5.5 ml) and perbenzoic acid (159 mg) in chloroform (2.5 ml) gave conduritol-C epoxide. A part of it had m.p.134-146°. (Preparation and purification of the epoxide are described in the experimental part of the next chapter.)

Conduritol-E epoxide: Conduritol-E (0.28 g), water (5 ml), acetic acid (15 ml) and perbenzoic acid (467 mg) in chloroform (11 ml) gave conduritol-E epoxide, 0.1 g (32%)(m.p.186-189°) and 0.18 g (58.7%)(m.p.175-176°).

Conduritol-F epoxide: Conduritol-F (0.17 g), acetic acid (10 ml), perbenzoic acid (272 mg) in chloroform (6.2 ml) gave conduritol-F epoxide, m.p.157-157.5°.

Analytical values of conduritol epoxides

Isomer	M.p.	Calcd. for $C_6H_{10}O_5$(162.1) C,44.44; H,6.22
A	112°	Found: C,44.26; H,5.90
B	155°	44.61; 6.52
C	136°	44.55; 5.98
E	176°	44.12; 6.40
	189°	44.69; 6.05
F	157.5°	44.58; 6.32

III. Deoxyinositols (Quercitols)

1. Historical

According to theory, ten deoxyinositols (four meso forms and six dl pairs (XX)-(XXIX) can be isolated.

(When the author refers to a racemic compound, only one arbitrarily chosen enantiomorph is shown in the figure.)

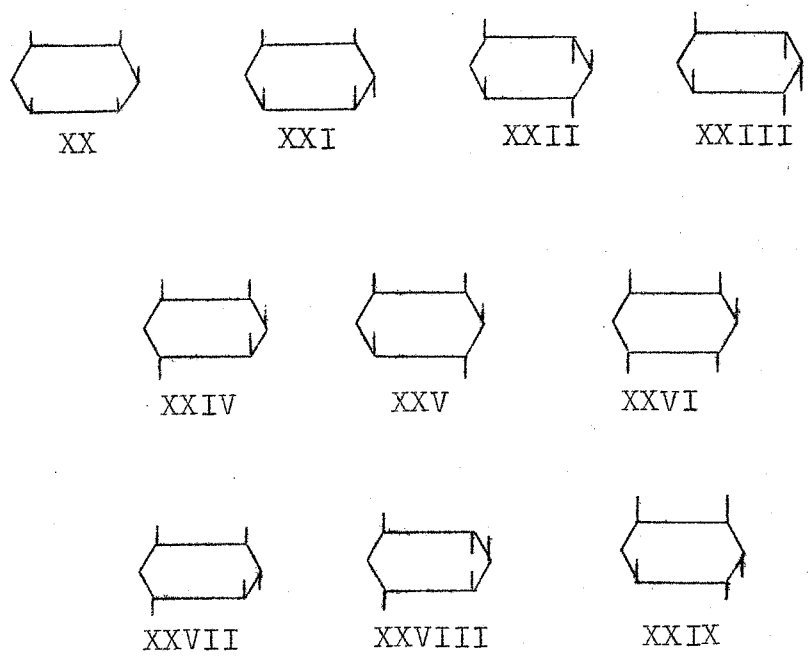


Fig.4 Deoxyinositols

(XX-XXIII : meso ; XXIV-XXIX : rac.)

Among them D-1-deoxy-muco-inositol (XXVIII) was named (+)-proto-quercitol by Angyal and Macdonald[35], which had been isolated by Braconnot[36] in 1849 and by Dessaignes[37] in 1851 from acorns (Quercus pedum culata and Quercus sessiliflora). One other cyclohexanepentol has been found in nature. Power and Tutin[38], who isolated it from

Gymnema sylvestre, named it "l-quercitol". Later, Hérissey and Poirot[39] isolated the same deoxyinositol but named it "viburnitol". In 1950, Posternak and Schopfer[40] established the identity of both substances and determined it D-1-deoxy-myo-inositol(XXVII).

Other deoxyinositols have been synthesized by several methods.

(1) In 1941, Posternak[28] obtained all-trans deoxyinositol (2-deoxy-myo-inositol (XXII))by catalytic hydrogenation of myo-inosose-2 using platinum oxide as catalyst in acetic acid-sulfuric acid solution. Since then, starting from several inositol isomers, some authors succeeded in synthesizing the following deoxyinositol isomers by similar methods: 5-deoxy-myo-inositol (XXIII)(neo-quercitol)[41], 2-deoxy-epi-inositol (XXV)((-) and (±)-epi-quercitol)[42][43] and l-deoxy-myo-inositol((+)- and (±)-vibo-quercitol; viburnitol)(XXVII)[26].

(2) Recently, Angyal and McHugh[24] isolated deoxy-cis-inositol (XX), 2-deoxy-epi-inositol (XXV) and 2-deoxy-myo-inositol (XXII) from the reaction mixture of catalytic hydrogenation of tetrahydroxy-

benzoquinone.

(3) McCasland and Horswill[13] prepared 1-deoxy-myo-(XXVII) and 2-deoxy-myo-inositol (XXII) from the corresponding bromodeoxyinositols which, in turn, were obtained by the action of acetyl bromide to myo-inositol. McCasland[44] also reported the synthesis of two deoxyinositols few months ago, the structure of which was determined as XXVI and XXIX (both are optically active). Very recently, he and three co-workers reported[44a] the study of these quercitols and another isomer (neo-quercitol, that is 5-deoxy-myo-inositol), the latter of which was prepared from 1,2-anhydro-neo-inositol (optically active) by direct reduction with hydrogen and Raney Nickel.

2. Systematic Synthesis

In the foregoing chapter, synthesis of conduritol epoxides was described. When reacting with HBr, each epoxide gave one or two bromodeoxyinositols which were easily convertible to deoxyinositols according to the McCasland's method. Thus the author prepared five stereoisomers of deoxyinositol in which all the hitherto unknown isomers are

included.

At first, the author carried out the reaction of conduritol epoxides with aqueous HBr to obtain seven stereoisomers of bromodeoxyinositol. Until that time, six stereoisomers of bromodeoxyinositol had been synthesized[45]. Kubler[10] had obtained bromohydrin of conduritol-A, and McCasland et al.[13][14] had prepared three bromodeoxyinositols from myo-inositol and epi-inositol. Recently, McCasland et al.[44][44a] reported to have obtained two new bromodeoxyinositols from optically active 1,2-anhydro-allo-inositol (XI). The isomers obtained by the author were unknown except one, and all bromodeoxyinositols known at present are shown in the following table. (p. 37)

From conduritol-A epoxide, only one bromodeoxyinositol (decomp.p.191.5°) was obtained quantitatively. As the structure of this epoxide was established as 2,3-anhydro-allo-inositol (epoxide ring is cis to the neighboring hydroxyl group)[33], the bromodeoxyinositol obtained must be 5-bromo-5-deoxy-rac-inositol (XXX). Its pentaccetate gave

conduritol-E tetraacetate on zinc-acetic acid treatment. This confirms its structure.

Conduritol-B epoxide gave 2-bromo-2-deoxy-rac-inositol (XXXI), one of the known[13] isomers, in 78% yield. One other known isomer theoretically possible to be produced was not obtained, probably because of predominant diaxial opening[46] of the epoxide ring. (cf. the last chapter.)

There are two possible isomers in conduritol-C epoxide (see Table 6): 1,2-anhydro-neo-inositol (IX) and 1,2-anhydro-epi-inositol (X). Crude crystals obtained by epoxidation of conduritol-C gave, after repeated recrystallization with ethanol, crystals of m.p. 144-146° (m.p. of tetraacetate; 114-115°) and a syrup (m.p. of tetraacetate; 115.5-116.5°).

Reacting with HBr, the crystalline epoxide gave two unknown bromodeoxyinositols, one of which (m.p. of pentaacetate;139-140°) was shown to be 1-bromo-1-deoxy-allo-inositol (XXXII) by the fact that it, on hydrogenolysis, gave 1-deoxy-allo-inositol (XXVI). Accordingly, another isomer (m.p. of pentaacetate;209-210°) should be 5-

Table 7. Bromodeoxyinositols.

Isomer (Configuration)(No.)	M.p. (Signal of opt. rot.)	M.p. of Ac_5
1-Br-1-deoxy-allo-(1234/56)(XXXII)	(syrup)	139-140°
5-Br-5-deoxy-allo-(1234/56)(XXXIV)	(syrup)	148-149°
3-Br-3-deoxy-muco-(1245/36)(XXXVI)		178-179°
5-Br-5-deoxy-myo- (1235/46)(XXXIII)		209-210°
1-Br-1-deoxy-neo- (123/456)(XXXV)	214° dec. 229° (-)*	
2-Br-2-deoxy-rac- (124/356)(XXXI)	160° 171°**	106.5-107.5° 108° & 125°**
5-Br-5-deoxy-rac- (124/356)(XXX)	191.5° dec. 203° (-)*	158-159°
4-Br-4-deoxy-myo- (1235/46)		151.5°***
Br-deoxy-scyllo- (135/246)	223°**	240°**

*Ref.44 and 44a. **Ref.13. ***Ref.14.

(There are three other isomers of unknown configuration derived from conduritol-A: Kubler's conduritol bromohydrin[10] and two bromohydrins obtained by the author. See below.)

bromo-5-deoxy-myo-inositol (XXXIII), and the original epoxide was proved to be 1,2-anhydro-neo-inositol (IX). This epoxide was also resulted by treatment of conduritol-E epoxide (XI) with alkali (epoxide migration[33]). This fact also confirms its configuration.

From the above experiments, another isomer is proved to be 1,2-anhydro-epi-inositol (X). When crude epoxide was acetylated, a new isomer of tetraacetyl-anhydro-inositol (m.p.115.5-116.5°) was gained, which must be tetraacetate of X.

On the other hand, crude crystals or a syrup obtained by recrystallization of the epoxide, on HBr treatment, gave an unknown isomer of bromo-deoxyinositol (m.p. of pentaacetate;148-149°). It must be 5-bromo-5-deoxy-allo-inositol (XXXIV), because the possible isomers of bromodeoxyinositol from 1,2-anhydro-epi-inositol are 4-bromo-4-deoxy-myo-inositol and 5-bromo-5-deoxy-allo-inositol (XXXIV), the former of which are already known.

Conduritol-E epoxide gave two bromodeoxyinositols, one of which was identical with 5-bromo-

5-deoxy-rac-inositol (XXX)(obtained already from conduritol-A). Consequently, the other isomer must be 1-bromo-1-deoxy-neo-inositol (XXXV).

From conduritol-F epoxide (2,3-anhydro-epi-inositol; It is not 1,2-anhydro-rac-inositol, because it gave myo-inosamine-4 by treatment with ammonia. Cf. the following chapter.)(XII) an unknown isomer of bromodeoxyinositol was isolated which was shown to be 3-bromo-3-deoxy-muco-inositol (m.p. of pentaacetate;178-179°)(XXXVI), because the another isomer theoretically possible to be formed is 4-bromo-4-deoxy-myo-inositol, which is a known substance (m.p. of pentaacetate;151.5-152.5°).

Reaction of bromine water to conduritols was also tried and some bromodeoxyinositols were isolated. They are listed in Table 8. (p. 41)

The first two unknown isomers in this table were both derived from conduritol-A. There are four possible isomers of conduritol-A bromohydrins. One is 5-bromo-5-deoxy-rac-inositol (XXX) which was already isolated and identified. Other possible

Fig. 5.

Synthesis of Deoxyinositols
through Bromodeoxyinositols

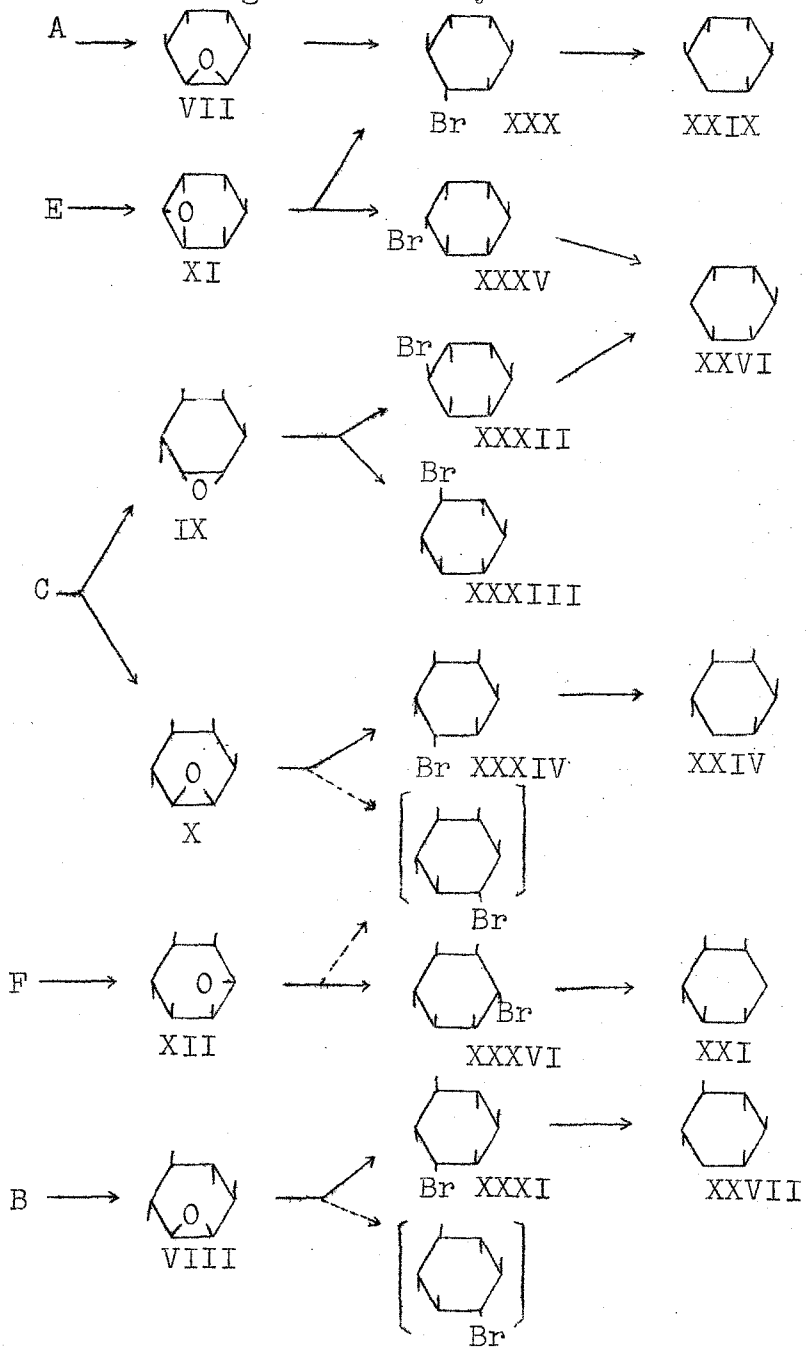


Table 8. Conduritol Bromohydrins.

Source (Conduritol)	M.p.	M.p. of Ac_5	Configuration
A	113°		(unknown)
A	206° dec.		(unknown)
A		159°	5-Br-5-deoxy-rac-I (XXX)
B		107°	2-Br-2-deoxy-rac-I (XXXI)
C		140°	1-Br-1-deoxy-allo-I (XXXII)
C		149°	5-Br-5-deoxy-allo-I (XXXIV)

three isomers are 1-bromo-1-deoxy-rac, 2-bromo-2-deoxy-allo-(cis-addition) and 1-bromo-1-deoxy-muco-inositol (cis-addition). The two isomers obtained now must be included in these three structures, and Kubler's bromohydrin (m.p.175°) also corresponds to one of these three.

Six of stereoisomeric bromodeoxyinositols thus obtained were submitted to catalytic hydrogenolysis under low pressure in the presence of Raney Nickel and anion exchange resin.

From bromodeoxyinositols of known configuration ((XXX), (XXXV) and (XXXI)), 2-deoxy-allo-inositol (XXIX), 1-deoxy-allo-inositol (XXVI) and 1-deoxy-myo-inositol (XXVII) were obtained respectively. The last compound was a known isomer[13)26)] and was compared and identified with authentic sample by m.p. and IR spectrum.

Bromodeoxyinositol (m.p. of pentaacetate; 140°) obtained from one of conduritol-C epoxide gave 1-deoxy-allo-inositol (XXVI) which showed the starting bromodeoxyinositol to be 1-bromo-1-deoxy-allo-inositol (XXXII) as described above. One other isomer (m.p. of pentaacetate; 149°) supposed to be 5-bromo-5-deoxy-allo-inositol (XXXIV) gave an unknown isomer of deoxyinositol. This fact confirmed the structure, because, if the substance were 4-bromo-4-deoxy-myo-inositol, it would give 2-deoxy-epi-inositol (XXV), a known isomer[42)]. This new deoxy-inositol is 1-deoxy-epi-inositol (XXIV). Last of all, 3-bromo-3-deoxy-muco-inositol (XXXVI) gave the last unknown isomer of deoxyinositol: 3-deoxy-epi-inositol (m.p. of pentaacetate; 168°)(XXI).

Table 9. Deoxyinositols.

Configuration	M.p. (Signal of opt. rot.)	M.p. of Ac_5	Ref.
1-deoxy-allo-(123/45)(XXVI)	225° dec.	169.5-171.5	*
	248° (+)	183° (+)	44,44a
2-deoxy-allo-(125/34)(XXIX)		90-92°	*
	258° (-)	117° (-)	44,44a
deoxy-cis- (12345) (XX)	240° dec.	163°	24
1-deoxy-epi- (1234/5)(XXIV)	262°	94°	44a
		88-91.5°	*
2-deoxy-epi- (1235/4)(XXV)	208°	143°	42,24
	194° (-)	125° (-)	43
3-deoxy-epi- (1245/3)(XXI)		167-168°	*
1-deoxy-muco-(134/25)(XXVIII)	237° (+)	(amorphous)	**
1-deoxy-myo- (124/35)(XXVII)	163°	114°	26,13,*
	181° (+)(-)	125° (+)(-)	26,40
2-deoxy-myo- (135/24)(XXII)	235°	190°	28,13
5-deoxy-myo- (15/234)(XXIII)	239°	182°	41,44a

* The author (Also cf. ref.45). ** Johansen, Ar., 209,243.

Experimental

(i) Opening of conduritol epoxides with HBr

5-Bromo-5-deoxy-rac-inositol (XXX) from conduritol-A epoxide.——Two hundred and eighty-four milligrams of conduritol-A epoxide (m.p.110°) were heated 1 hour with 10 ml of HBr (b.p.125°) on the boiling water bath. The resulted solution was dried up in vacuo to give a brown syrup, which was dissolved in a small portion of hot ethanol. After cooling, 407 mg (95.5%) of 5-bromo-5-deoxy-rac-inositol separated, m.p. 188-190° dec. After recrystallizations from ethanol/water (1:1), it melted at 190-191.5°. Anal. Calcd. for $C_6H_{11}BrO5$ (243.1): C,29.65;H, 4.56. Found: C,29.44;H,4.79.

Pentaacetyl-5-bromo-5-deoxy-rac-inositol.——One hundred and fifty milligrams of 5-bromo-5-deoxy-rac-inositol were heated for 1.5 hours with 3 ml of puridine and 3 ml of acetic anhydride on the boiling water bath. Evaporation of the ractants in vacuo gave a colorless residue, from which after recrystallization from ethanol 203 mg of prisms (73%) were obtained, m.p.155-157°.

After recrystallizations from ethanol the compound melted at 158-159°. Anal. Calcd. for $C_{16}H_{21}BrO_{10}$ (453.3): C,42.40;H,4.67;Br,17.63. Found; C,42.57; H,4.81;Br,17.84.

The crystals did not show any depression when mixed with pentaacetate of m.p.155-158° from conduritol-E epoxide.

Pentaacetyl-2-bromo-2-deoxy-rac-inositol from conduritol-B epoxide.——Two hundred and five milligrams of conduritol-B epoxide (m.p.154-155°) were treated with 10 ml of HBr as described above. The resulted syrup was acetylated using acetic anhydride and pyridine to give a crystalline product. Crystallization from ethanol gave 445 mg of pentaacetyl-2-bromo-2-deoxy-rac-insotitol (77.5%), m.p.100-104°. After recrystallization from ethanol, the product melted at 106.5-107.5° (prisms). It did not show any depression when mixed with pentaacetyl-bromodeoxyinositol of m.p. 108° from myo-inositol[13]. Anal. Calcd. for $C_{16}H_{21}BrO_{10}$ (453.3): C,42.40; H,4.67; Br, 17.63. Found: C,42.24;H,4.76; Br,17.48

2-Bromo-2-deoxy-rac-inositol(XXXI).——One hundred and sixty-nine milligrams of pentaacetyl-2-bromo-2-deoxy-rac-inositol were heated 1 hour with 3 ml of conc. HCl on the boiling water bath. Evaporation of the ractants in vacuo gave a syrup which was recrystallized from ethanol/benzene (1:1) to give 54 mg of crystals (60%), m.p.150°.

Conduritol-C epoxide (1,2-anhydro-neo-inositol (IX) and 1,2-anhydro-epi-inositol (X). ——Seven hundred and forty milligrams of conduritol-C (m.p.147-148°) in 67 ml of acetic acid were mixed with 26.8 ml of chloroform solution of 1.04 g of perbenzoic acid. After 3 days standing at room temperature, the solvent was evaporated in vacuo and the residue washed with ether several times. The resulted syrup was dissolved in boiling ethanol and the solution was concentrated and cooled. The first crude crystals of conduritol-C epoxide of m.p.125-140° separated gradually. The product weighed 490 mg (57.3%)

By repeated reactions as described above,

900 mg of the first crude crystals were obtained, which were recrystallized from ethanol to give 374 mg of 1,2-anhydro-neo-inositol of m.p.130-143°. The IR spectrum (in KBr) showed the following absorption maxima in the finger-prints area. 775, 820, 845, 890, 915 and 970 cm^{-1}. After more recrystallizations, the spectrum did not change. The pure product melted at 134-146°*. Anal. Calcd. for $C_6H_{10}O_5$(162.1): C,44.44;H,6.22. Found: C,44.55; H,5.98. *After dried for two weeks in the desiccator ($CaCl_2$), it melted at 144-146°.

When the mother liquor was concentrated and cooled, ca. 300 mg of crystals (mixture of the two anhydroinositols (a)) of m.p.110-127° separated. The characteristic bands of their IR spectrum (in KBr) were as follows, 775, 820, 845, 855, 880, 890 (shoulder), 915 and 970 cm^{-1}. (The crystals were used in the reaction described later without more purifications.)

Further recrystallizations of them from ethanol were not able to raise the m.p. For example, 269 mg of these crystals of m.p.110-127°, after

second recrystallization from ethanol, gave 140 mg of crystals melting at 115-121°. From this filtrate, a syrup (90 mg) (mixture of the two anhydroinositols (b)) was obtained.

Tetraacetyl-1,2-anhydro-neo-inositol.——Five milligrams of 1,2-anhydro-neo-inositol (m.p.138-140°)(The IR spectrum has no absorption at 855 and 880 cm^{-1}, the bands specficic for 1,2-anhydro-epi-inositol) were mixed with 1 ml of pyridine and 1 ml of acetic anhydride and set aside at room temperature. After 2 days, the reactants were evaporated in vacuo to give 6 mg of plates (59%) when the resulted syrup was rubbed with a few milliliters of ethanol/water (1:1). The product melted at 114-115° which did not change after recrystallizations. Anal. Calcd. for $C_{14}H_{18}O_9$(330.3): C,50.91; H,5.49. Found: C,51.17:H,5.57.

Tetraacetyl-1,2-anhydro-epi-inositol.—— Acetylation of 60 mg of crystals (m.p.130-131°), obtained from the first crude crystsls of conduritol-C epoxide gave 71 mg of prisms (57.5%) of

m.p.106-107° and 27 mg of plates (22%) of m.p.110°. The prisms melted at 115.5-116.5° (tetraacetyl-1,2-anhydro-epi-inositol) after more recrystalizations from ethanol, and gave a different IR spectrum from that of tetraacetyl-1,2-anhydro-neo-inositol. Anal. Calcd. for $C_{14}H_{18}O_9$(330.3): C,50.91;H,5.49. Found: C,51.03; H,5.67.

The IR spectrum of the plates was identical with that of tetraacetyl-1,2-anhydro-neo-inositol.

Pentaacetyl-1-bromo-1-deoxy-allo-inositol and pentaacetyl-5-bromo-5-deoxy-myo-inositol from 1,2-anhydro-neo-inositol.——Two hundred milligrams of 1,2-anhydro-neo-inositol were heated 2 hours with 8 ml of HBr on the boiling water bath. Evaporation of the reagents gave a yellow-colored syrup (ca.420 mg) which was treated with 5 ml of pyridine and 5 ml of acetic anhydride. Fifteen milligrams of pentaacetyl-5-bromo-5-deoxy-myo-inositol (2.7%) were obtained, m.p.189-193°(prisms). After recrystallizations from ethanol, it melted at 209-210°. Anal. Calcd. for $C_{16}H_{21}BrO_{10}$(453.3): C, 42.40;H,4.67. Found: C,42.42;H4.92.

The mother liquor of the prisms was evaporated and the residue heated with HCl in aqueous ethanol. Evaporation of the reagents gave a syrup, which was chromatographed on a cellulose powder column (23 cm x 1.5 cm) in acetone/water (4v:1v) solution. The eluate was fractionated to 50 drops portions (ca.2 ml) by using fraction collector.

The fractions 2 to 4, after evaporation and acetylation, gave 266 mg of needles (47.7%), m.p. 123°. The fractions 5 to 7 gave 32 mg of pentaacetyl-5-bromo-5-deoxy-myo-inositol (4%), m.p. 210°. (The total yield of this isomer is 47 mg (67%))

The needles, after recrystallizations from ethanol melted at 139-140°(pentaacetyl-1-bromo-1-deoxy-allo-inositol). Anal. Calcd. for $C_{16}H_{21}BrO_{10}$ (453.3): C,42.40;H,4.67;Br,17.63. Found: C,42.68; H,4.95;Br,17.83.

Pentaacetyl-5-bromo-5-deoxy-allo-inositol:

From the mixture of two anhydroinositols-(a). ——Four hundred and fourty-three milligrams of crystals (mixture-(a))(m.p.110-127°) were treated

with 10 ml of HBr as described above. The resulted syrup was chromatographed on a cellulose powder column (39cm x 4.5 cm) in acetone/water (4v:1v) solution. Every 200 drops portion (ca.7 ml) was collected by using fraction collector. From the faster moving syrup (fractions 33 to 40), after acetylation, 121 mg of pentaacetyl-1-bromo-1-deoxy-allo-inositol (9.7%), m.p.129-132°(needles), were obtained. From the slower moving fractions (fractions to 59), 51 mg of pentaacetyl-5-bromo-5-deoxy-allo-inositol (4.1%) crystallized after working up as described above. (m.p.144-147°, prisms)

Evaporation of other fractions left 310 mg of hygroscopic powder (46.6%)(two isomers) which were acetylated to give a mixture of two penta-acetylbromodeoxyinositols. From the mixture, only one isomer was isolated in crystalline form. For example, 42 mg of the powder gave 27 mg of prisms (34.5% from powder)(pentaccetyl-5-bromo-5-deoxy-allo-inositol), m.p.144-146°. Recrystallization from ethanol raised the melting point to 148-149°. Anal. Calcd. for $C_{16}H_{21}BrO_{10}$(453.3):C,42.40; H,4.67;

Br,17.63. Found: C,42.57;H,4.78;Br,17.62.

From the mixture-(b).——Ninety milligrams of syrup (mixture-(b))(cf. p.43) gave 26 mg of penta-acetyl-5-bromo-5-deoxy-allo-inositol (10.5%), m.p. 145-146° when treated as described above. From the filtrate a colorless syrup was obtained which did not crystallize.

5-Bromo-5-deoxy-rac-inositol (XXX) and 1-bromo-1-deoxy-neo-inositol (XXXV) from conduritol-E epoxide.——Three hundred and thirty-five milligrams of conduritol-E epoxide (m.p.176-177°) were heated 1.5 hours with 6 ml of HBr on the boiling water bath. After evaporation of the reagents in vacuo, and trituration with 3 ml of ethanol, 94 mg of 1-bromo-1-deoxy-neo-inositol (18.7%) separated soon, decomposing at 205-209°. Recrystallization from ethanol gave fine needles of dec.p.214°. Anal. Calcd. for $C_6H_{11}BrO_5$(243.1): C,29.65;H,4.56; Br,22.88. Found: C,29.88;H,4.57;Br,22.71.

From the filtrate, 237 mg of crystals (47.2%) of m.p.189-190°dec. separated after cooling. Recrystallizations from ethanol/water(4:1) did not

change the melting point. The IR spectrum in KBr was identical with that of bromodeoxyinositol from conduritol-A epoxide.

Evaporation of the filtrate of the crude crystals above left a syrup, from which after acetylation 36 mg of prisms (3.8%) of m.p.156.5-157.5° separated. The mixed m.p. with an authentic sample of pentaacetyl-5-bromo-5-deoxy-rac-inositol (m.p. 157°) did not show any depression. The IR spectra of the both compounds were also identical.

Pentaacetyl-3-bromo-3-deoxy-muco-inositol from conduritol-F epoxide.——(m.p.141.5°) were heated for 30 minutes with 3 ml of HBr on the boiling water bath. After evaporation of the reagents in vacuo and acetylation with pyridine and acetic anhydride, 47 mg of needles (60.5%) were obtained, m.p.176-178°. After recrystallizations from ethanol, pentaacetyl-3-bromo-3-deoxy-muco-inositol melted at 178-179°. Anal. Calcd. for $C_{16}H_{21}BrO_{10}$(453.4): C,42.40;H,4.67. Found: C,42.64;H,4.95.

(ii) Zinc decomposition of bromodeoxyinositol

Tetraacetyl-conduritol-E from pentaacetyl-5-bromo-5-deoxy-rac-inositol.——Two hundred and fourteen milligrams of pentaacetyl-5-bromo-5-deoxy-rac-inositol (m.p.155-158°) in 10 ml of acetic acid were mixed with 250 mg of zinc powder and heated for 7 hours at 100° with vigorous stirring. After that, undisolved material was filtered off and the filtrate evaporated in vacuo. The residue crystallized from ethanol giving 66 mg of plates (44.3%), m.p.138-145°. When mixed with authentic sample of tetraacetyl-conduritol-E, it did not show any depression. IR spectra of these crystals were also identical.

(iii) HBr elimination with alkali

Tetraacetyl-1,2-anhydro-epi-inositol from 5-bromo-5-deoxy-allo-inositol.——Seventy-eight milligrams of pentaacetyl-5-bromo-5-deoxy-allo-inositol in 3 ml of ethanol were heated for 3 hours with 2 ml of 20% HBr on the boiling water bath. Evaporation of the reagents gave a syrup (free 5-bromo-5-deoxy-allo-inositol), to which 2.62 ml of 0.0648N-NaOH (aq. soln.) were added, and the resulted

solution was set aside for 6 hours at 29°. After that the whole solution was dried up in vacuo (temp. below 50°) and the resulted viscous material was treated with 2 ml of pyridine and 1 ml of acetic anhydride. Undissolved material was filtered off and the filtrate evaporated in vacuo. When a few milliliters of dilute ethanol were added, 18 mg of crystals (32.1%) separated gradually, m.p.104-115°. The product showed an identical IR spectrum with that of tetraacetyl-1,2-anhydro-epi-inositol.

Tetraacetyl-1,2-anhydro-neo-inositol from penta-acetyl-1-bromo-1-deoxy-allo-inositol. ——— One hundred and fifty-five milligrams of penta-acetyl-1-bromo-1-deoxy-allo-inositol (m.p.140°) were heated with dil. HCl (10 ml) on the boiling water bath. After 2 hours, the reagents were evaporated off to give a syrup which was dried in the desiccator on NaOH. To the syrup, 5.25 ml of 0.065N-NaOH aq. solution were added and the solution was set aside 6 hours at room temperature (18°). Drying up in vacuo below 45° gave a syrup which was acetylated with pyridine and acetic

anhydride. The resulted syrup was triturated with aq. ethanol to give 15 mg of pentaacetyl-1-bromo-1-deoxy-allo-inositol (m.p. and mixed m.p.137-138°) (recovered). The filtrate of the crystals yielded 54 mg (47.8%) of tetraacetyl-1,2-anhydro-neo-inositol (m.p.110-115°). Identified by IR spectra and mixed m.p. (ca.112°).

(iv) Epoxide migration

Tetraacetyl-1,2-anhydro-neo-inositol from 1,2-anhydro-allo-inositol (conduritol-E epoxide).—— Two hundred milligrams of conduritol-E epoxide (m.p.180-186°) were dissoved in 4 ml of 0.5N-$Ba(OH)_2$ and set aside for 16 hours at room temperature (ca.25°). The solution, after running through a column of cation exchange resion (IR-120 H^+ form), was dried up in vacuo giving 280 mg of colorless syrup which did not crystallize. Heating of the syrup with pyridine and acetic anhydride on the steam bath, and drying up of the resulted solution gave a gummy substance, which crystallized from aq. ethanol. The crystals weighed 120 mg (29.4%)(m.p. and mixed m.p. with tetraacetyl-1,2-anhydro-neo-

inositol; 112°). IR spectrum of the product was identical with that of the latter. From the mother liquor, free anhydro-neo-inositol (m.p.143°) was obtained, IR spectrum of which was identical with that of 1,2-anhydro-neo-inositol. It weighed 27 mg (13.5%).

(v) Formation of conduritol bromohydrins

Conduritol-A bromohydrins.———

(1) One hundred and forty-seven milligrams of conduritol-A were dissoved in 8 ml of water and about 100 mg of bromine were added drop by drop to the solution. After two hours standing of the colorless solution at room temperature and 30 minutes heating at 100°, it was dried up in vacuo. A few drops of ethanol were added to the syrupy residue giving crude crystals which were recrystallized from ethanol/water. Crystals* weighed 58 ml (23.8%) and melted at 210° with decomposition (rectangular plates). The mother liquor of the crystals was dried up and the residue crystallized from ethanol to give 46 mg of crystals** melting at 180-181°.

Anal. Calcd. for $C_6H_{11}BrO_5$(243.1): C,29.65;H,4.56. Found*: C,29.45;H,4.42;**: C,48.55;H,6.76.

(2) One hundred and forty-six milligrams of conduritol-A were treated with bromine in water in a similar way as described above (but 4 hours standing at room temperature). Twenty-nine milligrams (11%) of leaflets were obtained, m.p.113-114°. Anal. Calcd. for $C_6H_{11}BrO_5$(243.1): C,29.65; H,4.56. Found: C,29.66;H,4.69. The filtrate of the crystals, after drying up and acetylation, gave 63 mg (13.7%) of pentaacetyl-5-bromo-5-deoxy-rac-inositol (m.p.149-155°). (Identified by IR spectrum)

(3) One hundred and forty-six milligrams of conduritol-A were mixed with 17 ml of 0.5% aq. solution of bromine and the resulted solution set aside for 26 hours at room temperature. Drying up and acetylation gave a syrup which crystallized from ethanol and weighed 85 mg (18.5%), m.p.153-154°. Mixed melting point with pentaacetyl-5-bromo-5-deoxy-rac-inositol showed no depression.

Conduritol-B bromohydrin.——From 146 mg of

conduritol-B (m.p.199-200°) in 10 ml of water and 35 ml of 0.5% aq. solution of bromine, 272 mg (60%) of pentaacetyl-2-bromo-2-deoxy-rac-inositol, m.p. 104-105°, were obtained after acetylation. Identified by mixed m.p. determination.

Conduritol-C bromohydrins.——From 137 mg of conduritol-C (m.p.148-152°) in 3.5 ml of water and about 100 mg of bromine, a colorless syrup resulted after standing for 7.5 hours at room temperature and drying up in vacuo. It was chromatographed on a cellulose powder column (35 cm x 4.5 cm) in acetone/water (4v:1v) solution. The eluate was fractionated to 200 drops portions (ca.7 ml) by using fraction collector. The fractions 28 to 38, after evaporation and acetylation, gave 93 mg of prisms (m.p.147-148°) and 42 mg (10%) of needles (m.p.138-139°). The slower moving fractions (39 to 59) gave 36 mg of prisms (m.p.147-148°) only. The total 129mg of prisms (31%) showed no depression when mixed with pentaacetyl-5-bromo-5-deoxy-allo-inositol. Similarly, the needles were shown to be pentaacetyl-1-bromo-1-deoxy-allo-inositol.

(vi) Catalytic hydrogenolysis of bromodeoxyinositols

Pentaacetyl-2-deoxy-allo-inositol from 5-bromo-5-deoxy-rac-inositol (XXX).——Three hundred and six milligrams of 5-bromo-5-depxy-rac-inositol in 40 ml of water were shaken for 1.5 hours with 500 mg of anion exchange resin (IR-4B) and 4g of Raney Nickel at a hydrogen pressure of 15kg/cm^2. After that, the catalysts were filtered off and the filtrate evaporated and the residue acetylated with pyridine and acetic anhydride. Trituration with ethanol/water of the resulted syrup gave 255 mg of pentaacetyl-2-deoxy-allo-inositol (54.1%), m.p. 87.5-89°. After recrystallization from ethanol gave prisms melting at 90-92°. Anal. Calcd. for $C_{16}H_{22}O_{10}$(374.4): C,51.33;H.5.92. Found: C,51.44; H,6.21.

Pentaacetyl-1-deoxy-allo-inositol from 1-bromo-1-deoxy-neo-inositol (XXXV).—— From 74 mg of 1-bromo-1-deoxy-neo-inositol (decomp.p.209°) in 30 ml of water with 200 mg of IR-4B and 1.2g of Raney Nickel, a syrup was obtained according

to the method as described above. When acetylated, it gave 80 mg of pentaacetyl-1-deoxy-allo-inositol (70.2%), m.p.168-169.5°. After recrystallization from ethanol, it melted at 169.5-170°(needles). Anal. Calcd. for $C_{16}H_{22}O_{10}$(374.4): C,51.33;H,5.92. Found: C,51.24;H,6.03.

1-Deoxy-allo-inositol (XXVI).——Seventy-seven milligrams of pentaacetyl-1-deoxy-allo-inositol(m.p. 169-170°) in 5 ml of ethanol were heated for 1 hour with 5 ml of conc. HCl on the boiling water bath. Evaporation of the reagents left 27 mg of 1-deoxy-allo-inositol (79%), decomp. p. 225°, which was not changed after recrystallizations from ethanol/water.

Pentaacetyl-1-deoxy-myo-inositol from 2-bromo-2-deoxy-rac-inositol[13] (XXXI).——From 223 mg of 2-bromo-2-deoxy-rac-inositol (m.p.160°) in 30 ml of water with 550 mg of IR-4B and Raney Nickel, a gummy substance was resulted after the reaction as described above. Acetylation of this product gave 202 mg of pentaacetyl-1-deoxy-myo-inositol (59.0%), m.p.64°(and after solidification 103°).

(needles). After recrystallization from ethanol, it melted at 112-113° [13)26)]. Anal. Calcd. for $C_{16}H_{22}O_{10}$(374.4): C,51.33;H,5.92. Found: C,51.39; H,5.84.

1-Deoxy-myo-inositol (XXVII).——From 89 mg of pentaacetate (m.p.103°) with HCl in aq. ethanol, 30 mg of 1-deoxy-myo-inositol (77%) crystallized, m.p.157-159°. After recrystallization from aq. ethanol gave prisms of m.p.158-159° [13)26)]. Anal. Calcd. for $C_6H_{12}O_5$(164.2): C,43.90;H,7.37. Found: C,43.76;H,7.36.

Pentaacetyl-1-deoxy-allo-inositol from pentaacetyl-1-bromo-1-deoxy-allo-inositol.——Ninety milligrams of pentaacetyl-1-bromo-1-deoxy-allo-inositol (m.p.134-136°) were hydrolyzed with dil. HBr. Evaporation of the reagents in vacuo left a syrup (ca.50 mg) which did not crystallize. The syrup was hydrogenated in 20 ml of water with 150 mg of IR-4B and 1.2 g of Raney Nickel as described above. The catalysts were filtered off and the filtrate was dried up in vacuo giving an

amorphous substance. When it was acetylated, 40 mg of needles (54.5%) were isolated, m.p.168-171.5°. Recrystallization from ethanol raised the melting point to 169.5-171.5°. When mixed with pentaacetyl-1-deoxy-allo-inositol from 1-bromo-1-deoxy-neo-inositol, it did not show any depression.
Anal. Calcd. for $C_{16}H_{22}O_{10}$(374.4): C,51.33;H,5.92. Found: C,51.54;H,6.21.

Pentaacetyl-1-deoxy-epi-inositol from penta-acetyl-5-bromo-5-deoxy-allo-inositol.——One hun-red and thirty-five milligrams of pentaacetyl-5-bromo-5-deoxy-allo-inositol (m.p.147-148°) were hydrolyzed with dil. HBr. The resulted syrup (ca. 80 mg) was hydrogenated in 30 ml of water with 300 mg of IR-4B and 1.2 g of Raney Nickel, as de-scribed above. When the catalysts were filtered off and the filtrate was dried up, a syrup was ob-tained. It was acetylated to give 63 mg of penta-acetyl-1-deoxy-epi-inositol (56.5%), m.p.88-90° (prisms). After recrystallization from water, it melted at 88-91.5°. Abal. Calcd. for $C_{16}H_{22}O_{10}$ (374.4): C,51.33;H,5.92. Found: C,51.45;H,5.90.

Pentaacetyl-3-deoxy-epi-inositol from pentaacetyl-3-bromo-3-deoxy-muco-inositol.——Seventy-nine milligrams of pentaacetyl-3-bromo-3-deoxy-muco-inositol (m.p.174-178°) were hydrolyzed with dil. HBr. The obtained syrup (ca.50 mg) was hydrogenated in 25 ml of water with 150 mg of IR-4B and Raney Nickel as described above. Filtration, evaporation and following acetylation gave 39 mg of pentaacetyl-3-deoxy-epi-inositol (60%), m.p.163-166° (rods). After recrystallization from ethanol, it melted at 167-168°. Anal. Calcd. for $C_{16}H_{22}O_{10}$ (374.4): C,51.33; H,5.92. Found: C,51.41;H,6.03.

IV. Inosamines

1. Historical.

Efforts to synthesize inosamines have been continuing since some of their isomers were found in nature.

The most popular inosamine of the natural origin is streptamine, an alkaline hydrolytic product of streptidine which is a component of streptomycin.[2] Strictly speaking, it is an inosadiamine; scyllo-inosadiamine-1,3.[47][48] The total syn-

thesis of it from myo-inositol[49] was attained already. Other naturally occurring inosamines are 2-deoxystreptamine and neo-inosamine-2. The former is a component of antibiotic "kanamycin",[4] neomycins[3] and paromomycin,[6] and the latter inosamine was found in hygromycin A,[5] and synthesized from myo-inososе-5 a few years ago.[51]

There have been four reported methods to introduce an amino-group into a cyclitol structure.

(1) Hydrogenation of inosose oxime or phenylhydrazone

Inosose oxime or phenylhydrazone available from inonose was submitted to Na-Hg reduction or catalytic hydrogenation. Inosamines obtained by these procedures are: epi-2,[42] myo-2,[50] myo-4,[48] neo-2,[51] scyllo-[52] isomers of inosamine and streptamine.[49]

(2) Cyclization of nitrodeoxyglucose.

In the course of preparing of inositols from aldose, Grosheintz and Fischer[25] cyclized 6-nitrodeoxyglucose and hydrogenated the product with hydrogen gas in the presence of Raney Nickel. Inosamines thus obtained were reported to be scyllo- and

muco-inosamine-3, the configuration of the latter of which had not been confirmed.

(3) Ammonolysis of bromodeoxyinositols

Wolfrom et al.[53] tried to react bromodeoxy-inositol mixture (2-bromo-2-deoxy-rac- and scyllo-) with liquid ammonia in an autoclave. They obtained two inosamines, rac-inosamine-2 and scyllo-inosamine, but in low yield.

(4) Ammonolysis of conduritol epoxides (anhydro-inositols)

Recently, Allen[54] prepared L(+)-1,2-anhydro-3,4,5,6-di-O-isopropylidene-allo-inositol and heated it with NH_3 in a steel bomb obtaining two inosamines: L-neo-inosamine-1 and L-inosamine-5.

2. Systematic Synthesis.

The author modified the last method, and synthesized eight inosamines from five conduritol epoxides.[55] This procedure provides a convenient and stereospecific synthetic route to inosamines which could be hardly gained by other methods, since we can prepare each isomer of conduritol epoxides, the starting material.

From conduritol-A epoxide, one inosamine was

isolated as its hexaacetate, the structure of which is rac-inosamine-5 (XXXVII), since the starting epoxide is 2,3-anhydro-allo-inositol (VII),[33] and the Walden inversion surely occurs during ammonolyzing epoxides.[54)56)]

Conduritol-B epoxide gave two inosamines; rac-inosamine-2 (XXXVIII) and scyllo-inosamine (XXXIX). The latter of them was identified by comparing with an authentic sample. The structure of the former had not been so concretely determined, as its first synthesis had been attained by ammonolysis of the mixture of bromodeoxyinositol isomers.[53] Since the possible isomers in the author's case were these two, and one of them was evidently determined as scyllo-inosamine (XXXIX), the other must be rac-inosamine-2 (XXXVIII). Reported melting point of its hexaacetate is the same as that of the author's product and this fact supports the identity of them.

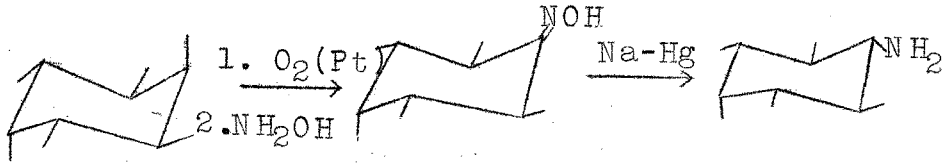
One of the conduritol-C epoxide, 1,2-anhydro-neo-inositol (IX), was submitted to ammonolysis. Two unknown inosamines (m.p. of Ac_6, 233° and 273°) were isolated, each of which must be either allo-inosamine-1 (XL) or myo-inosamine-5 (XLI).

The product having lower melting point (Ac_6; 233°) was gained in higher yield than the other isomer (30% vs. 10%). This suggested the former was allo-inosamine-1, if the diaxial opening rule (see the last chapter) could be applied to this case. Besides, lower melting point shown by the former was also suggesting that its configuration is less symmetric than the other.

The isomer having the higher melting point (Ac_6 273°) was supposed to be myo-inosamine-5, which has one axial hydroxyl group responsible to the catalytic dehydrogenation. Attempted oxidation and subsequent Na-Hg reduction, however, gave only recovered starting material (N-Acetylinosamine was recovered as hexaacetylinosamine).

On the other hand, myo-inosamine-5 was supposed to be gained from neo-inosose-2, a known inosose. neo-Inositol synthesized from conduritol-C was submitted to catalytic dehydrogenation. To neo-inosose-2 formed, which was not isolated, hydroxylamine hydrochloride and sodium acetate were added and hydrogenated with Na-Hg in a weakly acidic medium. After acetylation and purification by sublimation, a sub-

stance melting at 269° was obtained and showed an identical IR absorption with the hexaacetate of m.p.273°. Thus, the higher melting isomer was determined as hexaacetyl-myo-inosamine-5, and the other hexaacetyl-allo-inosamine-1.



neo-Inositol myo-Inosamine-5

Conduritol-E epoxide gave two inosamines, one of which was identical with rac-inosamine-5 (XXXVII) obtained from conduritol-A epoxide. Another isomer obtained should be neo-inosamine-1 (XLII) the optically active form of which had been synthesized by Allen.[54] The IR spectra of hexaacetates of the both substances were identical; that confirms the configuration of the author's product.

There are two possible isomers in conduritol-F epoxide; 2,3-anhydro-epi-inositol (XII) and 1,2-

anhydro-rac-inositol. On ammonolysis, the epoxide gave two inosamines, one of which was proved to be myo-inosamine-4 (XLIII) by comparing with an authentic sample (by L. Anderson[48]). Then the epoxide must be 2,3-anhydro-epi-inositol (XII) and the another inosamine obtained was supposed to be muco-inosamine-3 (XLIV). McCasland[48a] assigned one of the inosamines resulted by the cyclization of nitro-deoxyglucose[25] to muco-inosamine-3, but there was no crucial proof. Very recently (Apr. 23,1961), Lichtenthaler, an associate of Fischer, informed us that the inosamine gave two hexaacetates (m.p. 209° and 176°) which could be reversed to the starting inosamine. And that epi-inosamine-3 synthesized by another method was not identical with this isomer suggesting the possibility of the latter to be muco-inosamine-3. He also informed later (May 11, 1961) that one of the hexaacetates melting at 176° was shown to be identical with the author's hexaacetyl-muco-inosamine-3.

Melting points of those inosamines obtained by the author and their derivatives are shown in the following table.

Table 10

Inosamines synthesized by the auhhor

Inosamine (Configuration)(No.)	M.p.	M.p. of Ac_6
allo-1(1234/56)(XL)		231.5-233°
muco-3(1245/36)(XLIV)		177-178°
myo-4 (1235/46)(XLIII)*		236°
myo-5 (1235/46)(XLI)	173-195° dec.	271-273°
neo-1 (123/456)(XLII)**	240° dec.	241-242°
rac-2 (125/346)(XXXVIII)*		156-157°
rac-5 (125/346)(XXXVII)**	180-183°	189-191°
scyllo(135/246)(XXXIX)*		275-276°

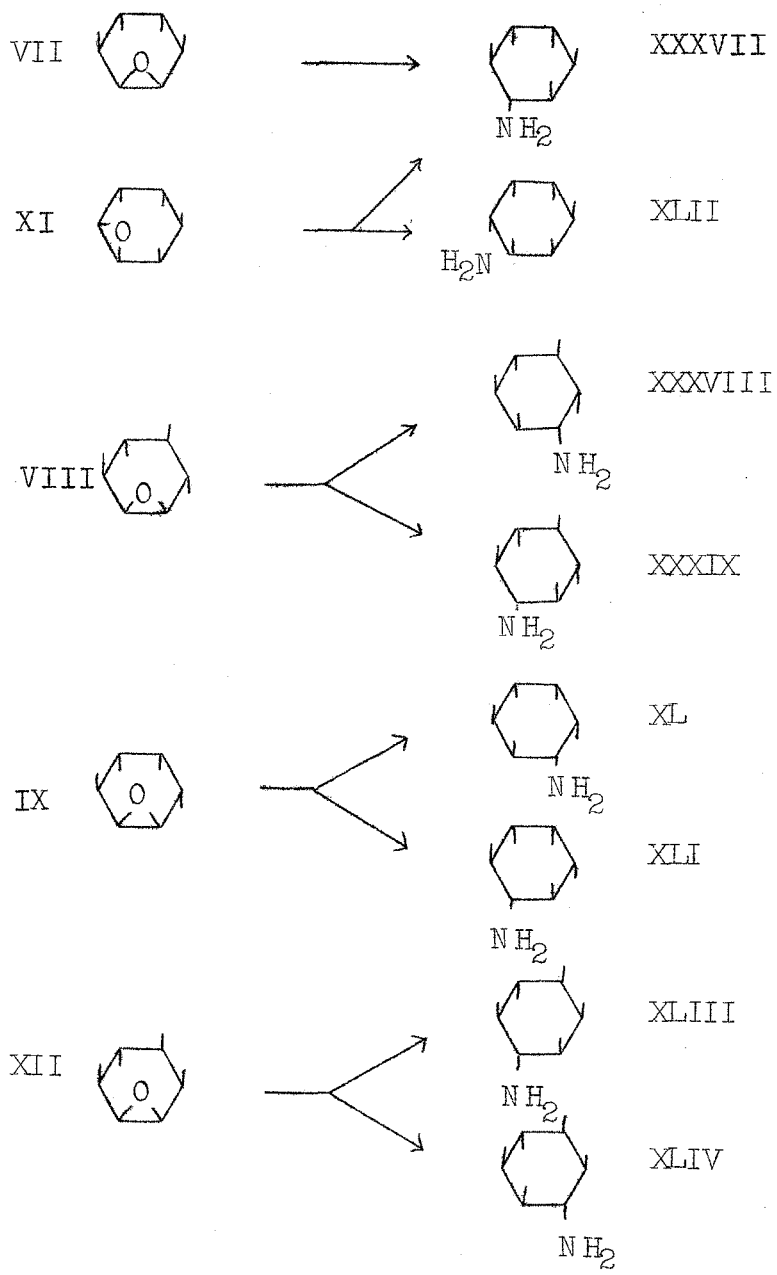
*known, Ref.48 and 53; **optical active forms are known, Ref.54.

N-Salicylidene or N-benzylidene derivatives of inosamines were also prepared and were shown to be convenient intermediates for separating the mixtures of isomers to each one.

The synthetic routes from conduritol epoxides of inosimines are summarized in the following figure.

Fig. 6.

Inosamines from conduritol epoxides



Experimental

Hexaacetyl-rac-inosamine-5 from conduritol-A epoxide———Two hundred and three milligrams of conduritol-A epoxide (m.p.111-112°) were heated for 5 hours with 15 ml of ammonia saturated absol. methanol in a sealed tube at 85-95°. Evaporation of the reaction mixture in vacuo left a syrup which, after dried, was acetylated with 4 ml of pyridine and 4 ml of acetic anhydride. After evaporation of the reagents in vacuo, the resulted syrup was dissolved in 3 ml of hot water and cooled to give 418 mg of hexaacetyl-rac-inosamine-5 (77.5%)(plates). After recrystallization from ethanol, the product melted at 189-191°. Anal. Calcd. for $C_{18}H_{25}NO_{11}$ (431.4): C,50.11; H,5.84; N,3.25. Found: C,49.86; H,5.94; N,3.53.

Hexaacetyl-scyllo-inosamine and hexaacetyl-rac-inosamine-2 from conduritol-B epoxide ——— Five hundred milligrams of conduritol-B epoxide (m.p.153-154°) were heated for 5 hours with 30 ml of ammonia saturated absol.methanol in a sealed tube at 90°. The crystalline residue (345 mg) was

obtained which was acetylated. The acetylated material was recrystallized from ethanol to give 58 mg of hexaacetyl-scyllo-inosamine*(7%)(needles), m.p.276°, and 525 mg of hexaacetyl-rac-inosamine-2**(67%)(prisms), m.p.156-157°. Anal. Calcd. for $C_{18}H_{25}NO_{11}$(431.4): C,50.11; H,5.84; N,3.25. Found:* *C,50,05; H,5.94; N,3.30. **C,50.21; H,5.90; N,3.36. (Hexaacetyl-scyllo-inosamine was prepared from myo-inositol by using Anderson's method.[52] Both substances showed identical spectra.)

N-Salicylidene-scyllo-inosamine and N-salicylidene-rac-inosamine-2_____ Four hundred and twenty milligrams of crude crystalline residue (scyllo-inosamine and rac-inosamine-2) in 10 ml of absol. ethanol were heated for 24 hours with 2 g of salicylaldehyde at 90°. When the solution was cooled, crystals separated, which were recrystallized from water to give 38 mg of N-salicylidene-scyllo-inosamine* (5.4%)(yellow plates), decomp.p. ca.240°, and 358 mg of N-salicylidene-rac-inosamine-2**(51.0%) (yellow needles), m.p.224-225°. Anal. *Calcd. for $C_{13}H_{17}NO_6 \cdot H_2O$(301.3): C,51.82; H,6.36. Found: C,50.41; H,6.37. **Calcd. for $C_{13}H_{17}NO_6$(283.3): C,55.12; H,6.05; N,4.95. Found: C,55.01; H,6.00;

N,4.96.

N-(O-Acetylsalicylidene)-penta-O-acetyl-rac-inosamine-2 ——— One hundred and thirty milligrams of N-salicylidene-rac-inosamine-2 were dissolved in a few milliliters of hot pyridine and, after cooled, mixed with 350 mg of acetic anhydride and set aside at room temperature overnight. The reaction mixture was poured into ice-water and extracted with ether. The ethereal layer was washed with 1N-HCl, water, sat-$NaHCO_3$ and water again. After drying over Na_2SO_4, ether was distilled away to give crystals, which was recrystallized from ethanol. Two hundred milligrams of N-(O-acetylsalicylidene)-penta-O-acetyl-rac-inosamine-2 (95%), (needles), m.p.175-177°. Anal. Calcd. for $C_{25}H_{29}NO_{12}$(535.5): C,56.09; H,5.46; N,2.62. Found: C,56.05; H,5.59; N,2.72.

N-Salicylidene-penta-O-acetyl-rac-inosamine-2 ——— One hundred and seventy milligrams of N-(O-acetyl-salicylidene)-penta-O-acetyl-rac-inosamine-2 in 7 ml of dioxane were bubbled with dry HCl. After one hour bubbling and more two hours standing, the reaction mixture was concentrated. Gradually

crystals separated, which were recrystallized from ethanol to give 95 mg of N-salicylidene-penta-O-acetyl-rac-inosamine-2 (63%) (needles), m.p.193-194°. ($FeCl_3$ color reaction: positive). Anal. Calcd. for $C_{23}H_{27}NO_{11}$ (493.5): C,55.97; H,5.52; N,2.84. Found: C,55.94; H,5.61; N,2.97.

Hexaacetyl-allo-inosamine-1 and hexaacetyl-myo-inosamine-5 from 1,2-anhydro-neo-inositol (IX) _____ One hundred and fifty milligrams of 1,2-anhydro-neo-inositol were heated for 7 hours with 10 ml of ammonia saturated absol. methanol in a sealed tube at 90-100°. After the reaction mixture was set aside at room temperature for several days, small needles grew in the solution. They were collected and weighed 29 mg, m.p.175-195°dec. (hygroscopic). After acetylation and recrystallization from ethanol, they gave 42 mg of hexaacetyl-myo-inosamine-5 (10%)(prisms), m.p.271-273°*. From the filtrate of the hygroscopic crystals, 120 mg of hexaacetyl-allo-inosamine-1 (30%)(flakes), m.p. 229-233°** were obtained. Anal. Calcd. for $C_{18}H_{25}NO_{11}$ (431.4): C,50.11; H,5.84. Found: *C,50.17; H,5.73. **C,50.21; H,6.12.

Hexaacetyl-myo-inosamine-5 from neo-inositol

One hundred and fifty milligrams of neo-inositol were dissolved in 80 ml of water, and platinum-catalyst (prepared from 150 mg of $PtO_2 \cdot H_2O$) was added. To the suspension, mechanically stirred at 60-65°, air was drawn vigorously by means of an air compressor. After 3.5 hours stirring, the reduction value (determined according to Heyns[30]) amounted to ca.85%. The reaction was stopped, the catalyst was filtered off, and the filtrate dried up in vacuo. The residue was filled up to 9 ml and 1 ml of aqueous solution containing 200 mg of hydroxylamine hydrochloride and 250 mg of anhydrous sodium acetate was added. After standing overnight (Then, UV spectrum of this solution showed no maximum between 230 and 300 mμ.), 5g of 3% Na-Hg were added in small batches with magnetical stirring. In the course of the reaction, the pH was read with a glass electrode and was held between 6.0 and 6.5 by additions of glacial acetic acid. The amine solution was filtered from the mercury, acidified with a few milliliters of conc. HCl, and evaporated to dryness in vacuo. Drying in the desiccator and

the following heating with pyridine-acetic anhydride at 130° for 1 hour gave a dark colored solution which was evaporated in vacuo. When 10 ml of water were added and the resinous matters filtered off, the dark red solution resulted. After ether extraction, drying over Na_2SO_4 and evaporating to dryness, it gave a syrup. Twenty milligrams of crystals separated from it when triturated with 3 ml of ethanol, m.p. 236°(ca.208° softening). They showed an identical IR absorption with hexa-acetyl-myo-inosamine-5 from conduritol-C epoxide. After sublimation at 255-260°/10 mm Hg, they gave prisms, m.p. 263-269° (227° sintering). Mixed melting point determination with the isomer from conduritol-C epoxide (m.p. 265°) showed no depression.

neo-Inosamine-1 (XLII) and rac-inosamine-5 (XXXVII) from conduritol-E epoxide _____ Six hundred milligrams of conduritol-E epoxide were heated for 6 hours with 35 ml of ammonia saturated absol. methanol in a sealed tube at 100-105°. After standing overnight at room temperature, neo-

inosamine-1 separated which was hygroscopic (139 mg), decomp.p.240°. Concentration of the filtrate gave 500 mg of rac-inosamine-5, m.p. 180-183° which were also hygroscopic.

Hexaacetyl-neo-inosamine-1——— Fifty milligrams of neo-inosamine-1 were heated for 1 hour with 5 ml of pyridine and 5 ml of acetic anhydride on the boiling water bath. When the reagents were evaporated and the resulted crude crystals recrystallized from ethanol, 121 mg of hexaacetyl-neo-inosamine-1 (91%)(needles), m.p. 241-242°, were obtained. Anal. Calcd. for $C_{18}H_{25}NO_{11}$ (431.4): C,50.11; H,5.84. Found: C,50.00; H,5.77.

Hexaacetyl-rac-inosamine-5——rac-Inosamine-5 (m.p.170-180°) was mixed with pyridine and acetic anhydride and the resulted solution set aside for two days at room temperature. Evaporation of the reagents and recrystallization of the residue from ethanol gave hexaacetate (needles), m.p. 186-187°. Anal. Calcd. for $C_{18}H_{25}NO_{11}$(431.4): C,50.11; H,5.84. Found: C,50.23; H,5.81. The product did not show any melting point depression when mixed with hexa-

acetyl-rac-inosamine-5 from conduritol-A epoxide.

N-Salicylidene-neo-inosamine-1_____One hundred milligrams of neo-inosamine-1 in 5 ml of ethanol were heated for 25 hours with 800 mg of salicylaldehyde at 100-105°. After filtration of the undissolved material (85mg of unreacting neo-inosamine-1), the filtrate was set aside in the refrigerator. Nineteen milligrams of N-Salicylidene-neo-inosamine-1 separated as yellow crystals, m.p. 239° dec. Anal. Calcd. for $C_{13}H_{17}NO_6$ (293.3): C,55.12; H, 6.05. Found: C,54.85; H,6.26.

N-Salicylidene-rac-inosamine-5_____One hundred and eighty milligrams of rac-inosamine-5 in 5 ml of ethanol were heated for 25 hours with 1.45 g of salicylaldehyde at 80-90°. When the solution was cooled, crystals separated, which was recrystallized from 30 ml of methanol to give 187.5 mg of N-salicylidene-rac-inosamine-5 (74%)(yellow needles), m.p. 228-230° dec.

Hexaacetyl-muco-inosamine-3 and hexaacetyl-myo-inosamine-4 from conduritol-F epoxide (2,3-anhydro-epi-inositol (XII))_____One hundred and

sixty milligrams of conduritol-F epoxide were heated for 5.5 hours with 12 ml of ammonia saturated absol. methanol in a sealed tube. Evaporation of the reagents left 170 mg of an oily substance, which did not crystallize. After heating with pyridine and acetic anhydride and evaporation of the reagents, a brown oily substance was obtained. It was recrystallized from ethanol to give 220 mg of hexaacetyl-muco-inosamine-3*(52%)(plates), m.p. 177-178°. From the filtrate, 4 mg of needles (1%), m.p. 236°, were obtained. This substance showed an identical IR-spectrum with that of hexaacetyl-myo-inosamine-4 synthesized by L. Anderson. Anal. Calcd. for $C_{18}H_{25}NO_{11}$(431.4): C,50.11; H,5.84; H,3.25. *Found: C,50.29; H,6.09; N,3.14.

V. Stereochemical Interpretation of the Reactions in Preparing Cyclitols

1. Diaxial Opening of Epoxide and Diaxial Addition to Double Bond.

Predominant diaxial opening of steroid epoxides advocated by Fürst and Plattner[46] has been proved to be applicable to epoxides in other fields. In the reactions of cyclitol epoxides, also, there are observed similar tendencies.

In Table 5, the yields of inositols obtained by trans hydroxylation (epoxidation and hydrolysis) of conduritols are listed. Several instances show that there are great unequalities in the yields of inositols. Conduritol-B, -C and -F gave rac-, allo-, and muco-inositol in much higher yields than scyllo-, myo-, and again myo-inositol respectively. Favored conformations of hydroxyl groups of the starting conduritol epoxides are: conduritol-B epoxide eeee, -C eaee, -F eeea. If the epoxides reacted with acid retaining these conformations, and diaxial opening was predominant in each case, all the results mentioned above are completely understandable. In other reactions such as HBr scission and ammonolysis, epoxides showed similar results. They are shown in Table 11.

Table 11.

Yields of isomeric pairs

Conduritol epoxide		(a) Bromodeoxyinositol and (b) Inosamine (%)	
B (eeee)	rac-2 (eeeeaa)	(a) 78:0 (b) 67:7	scyllo- (eeeeee)
C (eaee)	allo-1 (eaeeaa)	(a) 48:7 (b) 30:10	myo-5 (eaeeee)
F (aeee)	muco-3 (aeeeaa)	(a) 61:0 (b) 52:1	myo-4 (aeeeee)

_ ..... Conformations of newly introduced groups.

In the case of conduritol-E epoxide, the situation is somewhat different, as it can take two conformations of comparable stability (aeea and eaae). So that, the yields of two products in the three reactions seem to be rather irregular (Table 12).

Table 12.

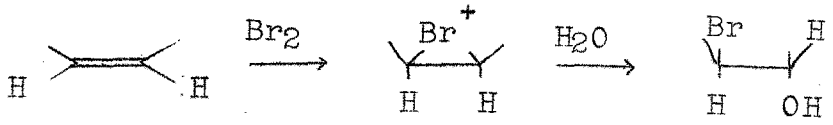
Isomers from conduritol-E epoxide

(Bromo-=Bromodeoxyinositol; Amine=Inosamine)

		Inositol	Bromo-	Amine
aeea	rac(-5) (aeeaaa ⇌ eaaeee)	27%	51%	75%
E ↓↑				
eaae	neo(-1) (eaaeaa ⇌ aeeaee)	44%	18%	21%

There might be such other factors controlling yields of isomers as van der Waals' radii of reaction species (H_3O^+, Br^- etc.). The results shown in Table 12 cannot be exactly explained by the data available now.

Diaxial addition to double bond was also observed. As shown in Table 8, conduritol-B and -C reacting with bromine-water gave bromodeoxyinositols of known configuration. They were obtained in rather high yield and diaxial addition can explain the reaction tendency. Action of hypobromous acid to double bond was reported[58] to follow such a sequence as described below.



This sequence is similar to epoxide opening reaction and such an electrophilic reaction as described above naturally causes higher yields of diaxial addition products.

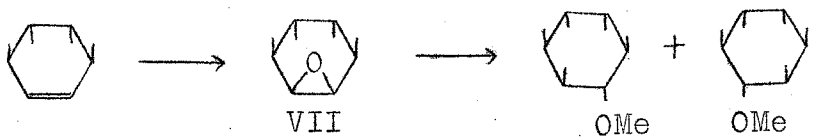
For example, from conduritol-C, the author isolated only two isomers, 1-bromo-1-deoxy-allo-inositol (XXXII)(10%) and 5-bromo-5-deoxy-allo-inositol (XXXIV)(31%) both of which were diaxial addition products, though there are four possible addition products in all. In the case of conduritol-B, we could see the same tendency: Only one isomer was isolated in 60% yield, which is 2-bromo-2-deoxy-rac-inositol, formed by diaxial addition.

2. Neighboring Group Participation in Epoxidation.

When conduritol-A and -F were treated with perbenzoic acid, two epoxides were assumed to be isolated. On the contrary to the expectation, only one isomer could be obtained from each

conduritol.

Angyal and Gilham[33] obtained (±)-pinitol (XLV) from conduritol-A epoxide with sodium methoxide, and determined the configuration of this epoxide as 2,3-anhydro-allo-inositol (VII). Thus the epoxide ring is situated cis to the neighboring hydroxyl groups.

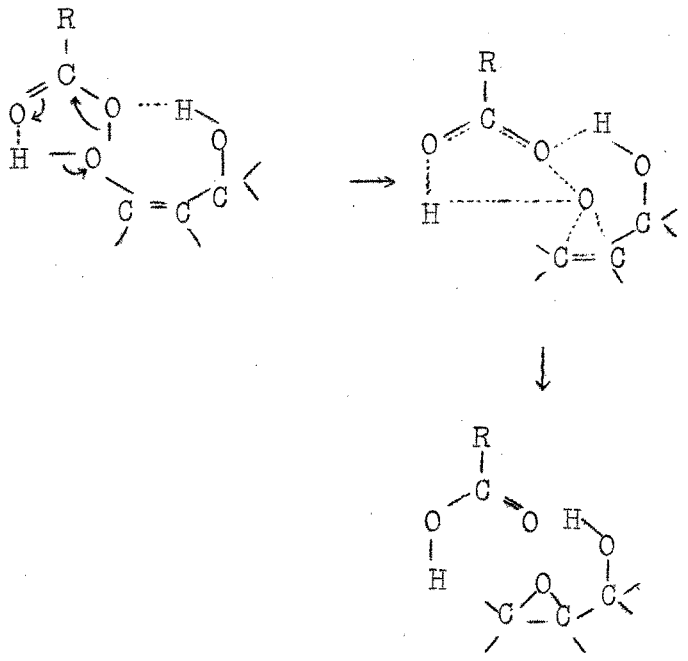


VII XLV

The structure of conduritol-F epoxide was established as 2,3-anhydro-epi-inositol in which, again, epoxide ring is cis to the neighboring hydroxyl groups.

These results are consistent with the results of epoxidation of other cyclic allylic alcohols which was studied especially by Henbest et al.[59] Based upon some experiments (e.g., epoxidation of 2-hydroxycyclohexene-1, 2-acetoxycyclohexene-1 etc.), they concluded that epoxidation occurred favorably cis to the allylic hydroxyl group, because the hydrogen bond between hydroxyl-hydrogen and peracid-

oxygen caused such results. The mechanism was illustrated as below.



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